SCIENTIFIC ABSTRACT

In the United states an estimated 25,400 new cases of ovarian cancer will be diagnosed, and approximately 14,500 women are expected to die from their disease in 1998. Mutations in the p53 suppressor gene has been reported in as many as 50-80% of ovarian carcinomas. *In vitro* studies with human cancer cells have shown that delivery of wild-type p53 by SCH 58500 into cells mutant or null for p53 results in a dose-dependent inhibition of cell proliferation; frequently associated with cell death via apoptosis.

Current standard treatment for ovarian cancer includes surgery to remove all or as much of the tumor as possible, followed by combination chemotherapy. A paclitaxel/cisplatin combination is a commonly used front line regimen. In patients who receive first line chemotherapy the response rate is 70% and the 5 year survival is 55%. Chemotherapy is curative in less than half of the patients and further therapy for this disease is needed. The rationale for intraperitoneal administration of SCH 58500 is based on the fact that disease is commonly confined to the abdominal cavity. Regional delivery provides increased exposure to the tumor with minimal exposure to normal tissues.

SCH 58500 is a recombinant adenoviral vector containing the cloned human wild-type (normal) tumor suppressor gene p53. The adenovirus has been rendered replication-deficient through deletion of the adenoviral E1 region. The design of this study incorporates the knowledge gained by the pre-clinical toxicology and pharmacology programs and Clinical Phase I studies. In 150 patients dosed to date, using 3 different routes of administration (intrahepatic artery, intraperitoneal and intratumoral), SCH 58500 has been well tolerated. Based on the Phase I shedding data, we believe SCH 58500 to be safe to the environment and health care workers. Transgene expression has been consistently seen, by RT-PCR in post dosing tissue biopsies or ascites cytospin. The risk benefit ratio favors the potential for clinical effect.

Since the vector is replication deficient and there is no evidence, preclinical or clinical, that overexpression of the gene confers risk to the host, and based on preliminary results of Phase I, this therapeutic approach is warranted. Further, there is significant potential for improved response when p53 is combined with standard therapy.

The objective of the study is to confirm that p53 in addition to standard chemotherapy is superior to chemotherapy alone. The target patient population for this trial is newly diagnosed ovarian and primary peritoneal cancer patients. All patients will receive 6 cycles of standard chemotherapy with half of the patients randomized to receive the experimental p53 product. This is a randomized, open label, multicenter trial to be conducted worldwide.